

UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

ASTELLAS INSTITUTE FOR REGENERATIVE
MEDICINE, and STEM CELL & REGENERATIVE
MEDICINE INTERNATIONAL, INC.,

Plaintiffs and Counterclaim-Defendants,

v.

IMSTEM BIOTECHNOLOGY, INC., XIAOFANG
WANG, and REN-HE XU,

Defendants and Counterclaim-Plaintiffs.

C.A. NO. 1:17-cv-12239-ADB

PLAINTIFFS' ANSWER TO DEFENDANTS' AMENDED COUNTERCLAIMS

Plaintiffs Astellas Institute for Regenerative Medicine (“Astellas”) and Stem Cell & Regenerative Medicine International, Inc. (“SCRMI”) (collectively, “Plaintiffs”) hereby reply to the Amended Answer and Counterclaims of Defendants ImStem Biotechnology, Inc., (“ImStem”), Xiaofang Wang, and Ren-He Xu (collectively, “ImStem” or “Defendants”), D.I. 91, as follows:

Except as specifically admitted below, Plaintiffs deny any allegation contained in of Defendants’ Amended Answer and Counterclaims. Any factual allegation below is admitted only as to the specific admitted facts, not as to any purported conclusions, characterizations, implications, or speculations that may arguably follow from the admitted facts. This pleading is based upon Plaintiffs’ present knowledge as to its own activities, and upon information and belief as to the activities of others. To the extent that the headings or other non-numbered statements in Defendants’ Amended Answer and Counterclaims contain any allegations, Plaintiffs deny each and every allegation therein. Plaintiffs deny that Defendants are entitled to the relief requested or to any other relief.

COUNTERCLAIMS¹

NATURE OF THE ACTION

1. Plaintiffs admit that Astellas/SCMRI personnel reached out to Drs. Xu and Wang to establish a collaboration wherein Astellas/SCMRI personnel provided mesenchymal stem cells and related information to Drs. Xu and Wang so that Drs. Xu and Wang could test those cells in the Experimental Autoimmune Encephalomyelitis (EAE) animal model. Plaintiffs further admit that this collaboration lasted for a few years. Plaintiffs deny the remaining allegations of Paragraph 1.

2. Plaintiffs admit that Dr. Wang performed animal studies involving testing Plaintiffs' mesenchymal stem cells in the Experimental Autoimmune Encephalomyelitis (EAE) animal model. Plaintiffs further admit that Dr. Wang shared at least some of the data from these studies with Plaintiffs. Plaintiffs deny the remaining allegations of Paragraph 2.

3. Plaintiffs admit that they filed Provisional Patent Application No. 61/565,358 on November 30, 2011 claiming the method of using MSCs in a variety of treatments, including in autoimmune treatment. Plaintiffs further admit that Provisional Patent Application No. 61/565,358 contains the results of a pilot animal study to treat EAE using Plaintiffs' mesenchymal stem cells. Plaintiffs deny the remaining allegations of Paragraph 3.

PARTIES

4. On information and belief, Plaintiffs admit the allegations of Paragraph 4.
5. On information and belief, Plaintiffs admit the allegations of Paragraph 5.
6. Admitted.

¹ Plaintiffs have incorporated the headings that appear in Defendants' Counterclaims. Plaintiffs do not necessarily agree with the characterization of the headings and do not waive any right to object to those characterizations.

7. Admitted.

JURISDICTION AND VENUE

8. This Paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Plaintiffs do not contest that the Court has jurisdiction over the subject matter of the Counterclaims.

9. This Paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Plaintiffs do not contest that venue with respect to the Counterclaims is proper in this judicial district.

10. This Paragraph contains legal conclusions to which no answer is required. To the extent an answer is required, Plaintiffs do not contest personal jurisdiction in this Court for purposes of the Counterclaims.

BACKGROUND

Scientific Background

11. Plaintiffs admit that human embryonic stem cells are pluripotent and that, at some point, some human embryonic stem cells had been obtained from frozen human fertilized eggs. Plaintiffs further admit that ethical considerations have played a role in encouraging development of methods of growing stem cells in laboratories and in the study and research of stem cells in the treatment of various diseases. Plaintiffs deny the remaining allegations of Paragraph 11.

12. Plaintiffs admit that this case involves a protocol for making mesenchymal stem cells (also called “MSCs”) from human embryonic stem cells using a hemangioblast intermediate. Plaintiffs further admit that mesenchymal stem cells can differentiate into at least bone, cartilage, and adipose tissues. Plaintiffs deny the remaining allegations of Paragraph 12.

13. Plaintiffs admit that regenerative medicine involves using stem cells to rejuvenate, replace, or regenerate damaged tissues. Plaintiffs further admit that regenerative medicine therapies have the potential to heal diseased and degenerated tissues and organs. Plaintiffs further admit that researchers have been studying how stem cells, and particularly mesenchymal stem cells, can be used to treat a variety of degenerative conditions, including heart failure, autoimmune disorders, tissue damage, arthritis, and bone fractures. Plaintiffs deny the remaining allegations of Paragraph 13.

14. Admitted.

Factual Background

15. Plaintiffs admit that the experimental autoimmune encephalopathy (EAE) mouse model is a known mouse model of multiple sclerosis. Plaintiffs further admit that an EAE mouse develops paralysis over time, that this model is a close proximity mouse model for multiple sclerosis, and that white blood cells called lymphocytes are part of the inflammatory process that is a hallmark of multiple sclerosis. Plaintiffs lack knowledge or information sufficient to form a belief about the truth of the remaining allegations in this Paragraph, and thus denies them.

16. Plaintiffs admit that Dr. Shi-Jiang Lu worked at SCRMI at one point and that Dr. Lu knew Dr. Ren-He Xu. Plaintiffs lack knowledge or information sufficient to form a belief about the truth of the remaining allegations in this Paragraph, and thus denies them.

17. Plaintiffs admit that Dr. Shi-Jiang Lu suggested that Dr. Wang contact Dr. Erin Kimbrel to discuss a collaboration involving the hemangioblast-derived mesenchymal stem cells that Drs. Kimbrel and Lanza developed. Plaintiffs further admit that a July 2010 meeting between Dr. Lu and Drs. Wang and Xu is suggested in an email exchange. Plaintiffs deny the remaining allegations of Paragraph 17.

18. Denied.

19. Plaintiffs admit that they have been at the forefront of research regarding regenerative medicine and cell therapy for decades. Plaintiffs further admit that Drs. Kimbrel's and Lanza's research included the functionality of stem cells in treating degenerative conditions, such as autoimmune disorders. Plaintiffs deny the remaining allegations of Paragraph 19.

20. Plaintiffs admit that the quoted language in Paragraph 20 is part of an email from Dr. Kimbrel to Dr. Wang. Plaintiffs deny the remaining allegations of Paragraph 20.

21. Plaintiffs admit that Dr. Wang sent Dr. Kimbrel links to some papers in an email. Plaintiffs further admit that Dr. Wang's email includes a statement that "There are many labs have found some mechanism of how MSC suppresses immune function[.] There are some reviews out there." and that "Some report that hESC-MSC have stronger immunosuppressive activity than BM derived MSC, and some report show MSC can be introduced into mice for disease model. Both mouse and human MSC have been used to ameliorate EAE(an autoimmune disease). . . . Currently, no lab has tested the hESC-MSC to treat mouse EAE model yet." (Links omitted in quotation.) Plaintiffs deny the remaining allegations of Paragraph 21.

22. Plaintiffs admit that Dr. Kimbrel suggested that she and Dr. Wang meet in person to discuss the experimental design, methods for data collection, and other aspects of testing Drs. Kimbrel's and Lanza's hemangioblast-derived mesenchymal stem cells in the EAE model. Plaintiffs further admit that Dr. Kimbrel expressed interest in seeing whether Drs. Kimbrel's and Lanza's hemangioblast-derived mesenchymal stem cells had a positive effect in the EAE model. Plaintiffs deny the remaining allegations of Paragraph 22.

23. Plaintiffs admit that a meeting involving Dr. Kimbrel and Dr. Wang took place at SCRMI's Marlborough facility in August 2010. Plaintiffs deny the remaining allegations of Paragraph 23.

24. Plaintiffs admit that, at various times, Dr. Wang sent data from EAE experiments to Dr. Kimbrel. Plaintiffs further admit that Drs. Kimbrel and Lanza and Dr. Wang are listed as authors on a published journal article reporting results from EAE experiments involving Drs. Kimbrel's and Lanza's hemangioblast-derived mesenchymal stem cells. Plaintiffs deny the remaining allegations of Paragraph 24.

25. Plaintiffs admit that they did not provide access to the MA-09 hESC cell line to Dr. Wang. Plaintiffs further admit that Dr. Kimbrel provided Dr. Wang with her confidential protocol for making hemangioblasts from human embryonic stem cells, and for making mesenchymal stem cells from those hemangioblasts, and with confidential know-how regarding generation or culture of additional mesenchymal stem cells. Plaintiffs deny the remaining allegations of Paragraph 25.

26. Plaintiffs admit that Drs. Wang and Xu purport to have modified Plaintiffs' confidential protocols, but deny that those purported modifications were "their own" or meaningful. Plaintiffs deny the remaining allegations of Paragraph 26.

27. Denied.

28. Plaintiffs admit that they filed U.S. Provisional Patent Application No. 61/565,358 on November 30, 2011. Plaintiffs further admit that U.S. Provisional Patent Application No. 61/565,358 and U.S. Patent Application Nos. 13/691,349 and 13/905,526 contain the results of a pilot animal study to treat EAE using Plaintiffs' mesenchymal stem cells. Plaintiffs deny the remaining allegations of Paragraph 28.

29. Plaintiffs admit that the U.S. Patent and Trademark Office issued U.S. Patent Nos. 8,961,956 and 8,962,321. Plaintiffs further admit that both these patents claim priority to U.S. Provisional Patent Application No. 61/565,358. Plaintiffs deny the remaining allegations of Paragraph 29.

30. Plaintiffs admit that claim 1 of U.S. Patent No. 8,961,956 recites “A method for treating a disease or disorder, comprising administering to a subject in need thereof an effective amount of mesenchymal stromal cells or a preparation of mesenchymal stromal cells obtained by a method comprising culturing hemangioblasts under conditions that give rise to mesenchymal stromal cells.” Plaintiffs further admit that claim 3 of U.S. Patent No. 8,961,956 recites “The method of claim 1, wherein the disease or disorder is selected from multiple sclerosis, systemic sclerosis, hematological malignancies, myocardial infarction, organ transplantation rejection, chronic allograft nephropathy, cirrhosis, liver failure, heart failure, GvHD, tibial fracture, left ventricular dysfunction, leukemia, myelodysplastic syndrome, Crohn’s disease, diabetes, chronic obstructive pulmonary disease, osteogenesis imperfect, homozygous familial hypercholesterolemia, treatment following meniscectomy, adult periodontitis, vasculogenesis in patients with severe myocardial ischemia, spinal cord injury, osteodysplasia, critical limb ischemia, diabetic foot disease, primary Sjogren’s syndrome, osteoarthritis, cartilage defects, multisystem atrophy, amyotrophic lateral sclerosis, cardiac surgery, refractory systemic lupus erythematosus, living kidney allografts, non-malignant red blood cell disorders, thermal burn, Parkinson’s disease, microfractures, epidermolysis bullosa, severe coronary ischemia, idiopathic dilated cardiomyopathy, osteonecrosis femoral head, lupus nephritis, bone void defects, ischemic cerebral stroke, after stroke, acute radiation syndrome, pulmonary disease, arthritis, bone regeneration, inflammatory respiratory conditions, respiratory conditions due to an acute injury,

Adult Respiratory Distress Syndrome, post-traumatic Adult Respiratory Distress Syndrome, transplant lung disease, Chronic Obstructive Pulmonary Disease, emphysema, chronic obstructive bronchitis, an allergic reaction, damage due to bacterial pneumonia, damage due to viral pneumonia, asthma, exposure to irritants, tobacco use, atopic dermatitis, allergic rhinitis, hearing loss, autoimmune hearing loss, noise-induced hearing loss, psoriasis or any combination thereof.” Plaintiffs further admit that claim 4 of U.S. Patent No. 8,961,956 recites “The method of claim 1, wherein the disease or disorder is uveitis, an autoimmune disorder, an immune reaction against allogenic cells, multiple sclerosis, bone loss, cartilage damage, or lupus.” Plaintiffs deny the remaining allegations of Paragraph 30.

31. Plaintiffs admit that U.S. Patent No. 8,961,956 lists Erin Anne Kimbrel, Robert Lanza, Jianlin Chu, and Nicholas Arthur Kouris as inventors.

32. Plaintiffs admit that U.S. Patent No. 8,962,321 lists Erin Anne Kimbrel, Robert Lanza, Jianlin Chu, and Nicholas Arthur Kouris as inventors.

33. Plaintiffs admit that claim 17 of U.S. Patent No. 8,962,321 recites “The mesenchymal stromal cells of claim 14, wherein the mesenchymal stromal cells are mitotically inactivated.” Plaintiffs further admit that claim 18 of U.S. Patent No. 8,962,321 recites “The mesenchymal stromal cells of claim 17, comprising at least 10^6 mesenchymal stromal cells and a pharmaceutically acceptable carrier.” Plaintiffs further admit that claim 21 of U.S. Patent No. 8,962,321 recites “The composition of claim 14, wherein the mesenchymal stromal cells have a potency in an immune regulatory assay that is greater than the potency of bone marrow derived mesenchymal stromal cells.” Plaintiffs deny the remaining allegations of Paragraph 33.

COUNT I
(CORRECTION OF INVENTORSHIP FOR THE '956 PATENT, 35 U.S.C. § 256)

34. Plaintiffs hereby incorporate the answers set forth in response to Paragraphs 1 through 33.

35. Denied.

36. Denied.

37. Plaintiffs admit that they filed U.S. Provisional Patent Application No. 61/565,358 on November 30, 2011. Plaintiffs further admit that U.S. Patent No. 8,961,956 issued on February 24, 2015. Plaintiffs deny the remaining allegations of Paragraph 37.

38. Denied.

39. Denied.

40. Plaintiffs admit that Astellas intends to develop treatments of various diseases using the technology that is claimed in its patents, including the technology claimed in U.S. Patent No. 8,961,956. Plaintiffs deny the remaining allegations of Paragraph 40.

41. Denied.

COUNT II
(CORRECTION OF INVENTORSHIP FOR THE '321 PATENT, 35 U.S.C. § 256)

42. Plaintiffs hereby incorporate the answers set forth in response to Paragraphs 1 through 41.

43. Denied.

44. Plaintiffs admit that they filed U.S. Provisional Patent Application No. 61/565,358 on November 30, 2011. Plaintiffs further admit that U.S. Patent No. 8,962,321 issued on February 24, 2015. Plaintiffs deny the remaining allegations of Paragraph 44.

45. Denied.

46. Denied.

47. Plaintiffs admit that Astellas intends to develop treatments of various diseases using the technology that is claimed in its patents, including the technology claimed in U.S. Patent No. 8,962,321. Plaintiffs deny the remaining allegations of Paragraph 47.

48. Denied.

COUNT III
(UNJUST ENRICHMENT)

49. Plaintiffs hereby incorporate the answers set forth in response to Paragraphs 1 through 48.

50. Denied.

51. Plaintiffs admit that in the relevant time period SCRMI was a small company and did not have its own animal testing facilities. Plaintiffs deny the remaining allegations of Paragraph 51.

52. Plaintiffs admit that Dr. Wang sometimes sent data from the EAE experiments to Dr. Kimbrel. Plaintiffs further admit that in a December 9, 2010 email exchange, Dr. Kimbrel requested that Dr. Wang forward her a graph of data and that Dr. Wang replied attaching an excel file that contained a graph. Plaintiffs admit that Drs. Kimbrel and Lanza provided narrative text regarding the methods for generating mesenchymal stem cells for a grant application that was submitted around January 2011. Plaintiffs further admit that this grant application sought funding for studies to explore further the use of mesenchymal stem cells in the EAE model. Plaintiffs lack knowledge or information sufficient to form a belief about the truth of the remaining allegations in this Paragraph, and thus denies them.

53. Denied.

54. Plaintiffs lack knowledge or information sufficient to form a belief about the truth of the allegations in Paragraph 54, and thus denies them.

55. Plaintiffs lack knowledge or information sufficient to form a belief about the truth of the allegations in Paragraph 55, and thus denies them.

56. Denied.

57. Denied.

58. Plaintiffs admit that the U.S. Patent and Trademark Office issued U.S. Patent Nos. 8,961,956 and 8,962,321 based on the filing of provisional and non-provisional applications. Plaintiffs deny the remaining allegations of Paragraph 58.

59. Denied.

60. Denied.

61. Denied.

62. Denied.

63. Denied.

PLAINTIFFS AFFIRMATIVE DEFENSES

Plaintiffs assert the following affirmative and other defenses without prejudice to their right to plead additional defenses as discovery progresses.

FIRST AFFIRMATIVE DEFENSE **(Failure to State a Claim)**

The Counterclaims fail to state a claim upon which relief may be granted.

SECOND AFFIRMATIVE DEFENSE **(Unclean Hands)**

The Counterclaims are barred, in whole or in part, by the doctrine of unclean hands.

THIRD AFFIRMATIVE DEFENSE **(Statute of Limitations)**

The Counterclaims are barred, in whole or in part, by the applicable statute of limitations.

JURY DEMAND

Pursuant to Federal Rule of Civil Procedure 38(b), Plaintiffs hereby demand a jury trial on all claims so triable herein.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request the following relief:

- A. That the Court deny all the relief sought by Defendants in its Answer, Defenses and Counterclaims;
- B. That the Court dismiss with prejudice each and every one of the Counterclaims;
- C. That Defendants take nothing by their Counterclaims;
- D. That the Court award Plaintiffs the relief sought in its Complaint;
- E. That the Court award Plaintiffs the attorney's fees and costs incurred in this action; and
- F. That the Court award such other and further relief as it may deem just and proper.

Dated: September 6, 2019

Respectfully submitted,

/s/ David P. Frazier

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CERTIFICATE OF SERVICE

I hereby certify that this document, which was filed with the Court through the CM/ECF system, will be sent electronically to all registered participants as identified on the Notice of Electronic Filing, and paper copies will be sent via first class mail on September 6, 2019 to those identified as non-registered participants.

/s/ David P. Frazier

David P. Frazier